REMARKS

Claims 1-5 and 12-27 are pending in the present application. Claims 14-18 and 20-22 are withdrawn from consideration as being drawn to a non-elected invention. Applicants will cancel these claims upon indication of allowable subject matter in this application.

Claim 6 has been canceled without prejudice. The subject matter of claim 6 has been included in claim 1.

Claims 1 and 12-13 have been amended for greater clarity and to define the invention more particularly. Support for the claim amendments can be found throughout the specification (see, e.g., original claim 6). Withdrawn claims 14-15 have been amended to correct claim dependency. No new matter has been introduced.

Claims 24-27 have been added. Support for new claims 24-25 can be found, for example, on page 14, lines 21-32; and page 41, lines 1-14. Support for new claims 26-27 can be found, for example, on page 5, lines 28-29; page 15, lines 1-12; and Examples 12-16 on pages 37-42. No new matter has been introduced.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action mailed March 24, 2005.

Applicants note that the Examiner has rejoined claims 1-13 (wherein claims 7-11 have been canceled) with claims 19 and 23 for examination on the grounds that Applicants' argument in the Response and Amendment filed on May 24, 2004 is found persuasive.

Applicants further note that the Examiner has withdrawn the rejections under 35 U.S.C. § 102(a) and § 102(b) in view of Applicants' Response and Amendment filed on May 24, 2004.

Claim Rejections under 35 U.S.C. § 101 and § 112, 1st Paragraph

Claims 1-6, 12-13, 19, and 23 have been rejected under 35 U.S.C. § 101 because the claimed invention is allegedly "not being supported by either a specific, substantial utility, and credible asserted utility or a well established utility." The Examiner further rejects these claims under 35 U.S.C. § 112, first paragraph, for the same reasons. Applicants respectfully traverse these rejections for the reasons that follow.

Applicants reiterate the arguments already made of record. Applicants further provide herewith evidence showing that the claimed miniature proteins not only bind to a Bcl2 protein, but also promote apoptosis. They clearly have utility in the treatment of apoptosis-associated diseases. See the enclosed Declaration of Dr. Alanna Schepartz Shrader (the Declaration). The evidence presented in the Declaration demonstrates that the claimed miniature proteins induce apoptosis when introduced into mammalian cancer cells. For example, the results shown in **Exhibit B** demonstrate that the Bcl2-binding miniature proteins (e.g., PPBH3-1 and PPBH3-5) exhibited comparable or higher apoptosis-promoting activity in HeLa cells relative to that of Bak_{72-88} (a known death agonist served as a positive control). Applicants note that PPBH3-1 is described in the present application (see, e.g., Figure 4, PPBH3 is referred to therein as "4099"). The evidence provides clear support for the ideas recited in the specification that "these miniature proteins have therapeutic uses in the treatment of disease associated with the presence of a particular DNA or protein" (e.g., on page 22, lines 23-28). Specifically, the claimed invention has utility in the treatment of Bcl2-associated (e.g., apoptosis-associated) diseases including cancer, autoimmunity, and neurodegenerative disorders.

At the time the present application was filed, it was known in the art that Bcl2 and Bcl-X_L are antagonists of apoptosis, and that Bak induces apoptosis by binding to Bcl2 and Bcl-X_L through its BH3 domain. Both the Declaration and the present application provide evidence that the claimed miniature proteins function as highly potent and specific ligands for Bcl2 proteins. In particular, miniature proteins such as PPBH 3-2, PPBH3-3, and PPBH3-1 bind to Bcl2 with about 100-fold higher affinity than of Bak_{72-88} (a natural Bcl2-binding

ligand) binds Bc12. See **Exhibit A**, Figure 3(b); and the instant specification, on page 41, lines 1-10. Accordingly, in view of the teachings of the specification and the knowledge in the art, a skilled artisan would appreciate that these miniature proteins are functional equivalents of Bak and would promote apoptosis by binding to and antagonizing Bcl2 or Bcl-X_L. The claimed invention has a substantial and credible utility at least in the treatment of Bcl2-associated diseases (e.g., cancer).

In addition, both the Declaration and the present application show that the claimed miniature proteins specifically bind to a Bcl2 protein. For example, PPBH3-1 showed poor binding ability to other proteins such as calmodulin, protein kinase A (PKA), and carbonic anhydrase II. See **Exhibit A**, Figure 4(b); the present specification, on page 41, lines 15-22. Furthermore, Applicants' results demonstrate these miniature proteins exhibited high paralog specificity between Bcl2 family members (see **Exhibit C**). For example, PPBH3-1 and Bak_{72-88} preferentially bind to Bcl-X_L, and PPBH3-5 and PPBH3-6 preferentially bind to Bcl2. Accordingly, the utility of the claimed invention is specific.

In sum, it is clear that the present invention is indeed supported by a specific, substantial, and credible utility, particularly as to certain Bcl2-associated diseases due to abnormal apoptosis (e.g., cancer). Accordingly, Applicants have satisfied the requirements under 35 U.S.C. § 101. Reconsideration and withdrawal of the rejections are respectfully requested.

For the same reasons as described above, Applicants have also satisfied the enablement requirements under 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, 2nd paragraph

Claims 1-6, 12-13, 19, and 23 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Specifically, the Office Action asserts that "[c]laim 1 and all claims dependent therefrom, as written, are confusing because they embrace more than the elected invention . . . Applicants are requested to amend the claims so that they reflect the elected invention [SEQ ID NO: 23]" (Office Action, page 6, lines 2-6).

Solely to expedite prosecution, Applicants have amended independent claim 1 to clarify that "said at least one substituted residue is selected from a site on a known protein through which interaction with a Bcl2 protein occurs, wherein said avian pancreatic polypeptide binds to the Bcl2 protein."

Applicants note that the term "Bcl2 protein" in amended claim 1 is readily understood in the art to refer to any member of the Bcl2 family, which includes Bcl2 protein and other Bcl2 family members such as Bcl-X_L, Bid, Bax, Bad, and Bak. For example, the specification teaches that the claimed aPP miniature protein binds to both Bcl2 and Bcl-X_L (e.g., page 14, lines 21-32; page 41, lines 1-14). This finding is further supported by the inventors' own paper (**Exhibit A**). In addition, the Bcl2 family was well known at the time the application was filed (see, e.g., page 39, lines 13-15). Also see, e.g., Sattler et al., 1997 (enclosed as **Exhibit 1** in the prior response; also cited in the specification on page 14, lines 16 and 22-23) and Adams et al., 2001 (enclosed as **Exhibit 2** in the prior response). Accordingly, the term "Bcl2 protein" is clear and definite. A skilled artisan would have readily known that the term Bcl2 includes other Bcl2 family members as well as Bcl2.

Seven sequences (SEQ ID NOs: 23-29) are shown in Figure 4; they correspond to 4100, 4101, 4099, 4102, and the three unnamed sequences at the bottom, respectively. The sequence alignment in Figure 4 clearly shows that these seven sequences are highly conserved, differing from each other by only a few nucleotides. In addition, these seven sequences (SEQ ID NOs: 23-29) all relate to Bcl2-binding miniature proteins and are isolated from a BAKLIB phage library (see, e.g., Examples 12-16 on pages 37-42). Thus, SEQ ID NOs: 23-29 belong to the same invention recited in independent claims 1 and 19.

Further, Applicants note that one skilled in the art would readily appreciate that the term "known protein" of amended claim 1, when read in the context of claim 1 and the specification, refers to a known Bcl2-binding protein. It was known in the art that the Bcl2 family members bind to each other (homodimerize or heterodimerize), dependent claim 12 specifies that the known protein is a Bcl2 protein, which as described above, is understood in the art to refer to any member of the Bcl2 family (e.g., Bak, Bcl-X_L, Bid, Bax, Bad, and Bak). Indeed, the specification teaches use of Bak as a known protein for making the avian pancreatic polypeptide (aPP) miniature protein. Applicants present in the Declaration additional data (enclosed herewith as **Exhibit D**) that shows that another Bcl2 family member, Bad (like Bak, a known Bcl2-binding protein), can be effectively used for making Bcl2-binding miniature proteins as claimed by the present invention. Thus, the "known protein" of the claimed invention should not be limited to Bak.

In view of the above, Applicants submit that claim 1 as amended is a genus claim linking species (i.e., related Bcl2-binding miniature proteins including SEQ ID NO: 23). Although Applicants elected SEQ ID NO: 23 as a species for search purposes, Applicants respectfully remind the Examiner that, in accordance with MPEP 809, "should any linking claim be allowed, the restriction requirement must be withdrawn."

In sum, Applicants submit that amended 1 and its dependent claim are clear and definite to one of skill in the art. Reconsideration and withdrawal of rejection of claim 1 and claims dependent therefrom under 35 U.S.C. § 112, second paragraph, are respectfully requested.

The Office Action also asserts that "[c]laims 1, 19, and all claims dependent therefrom recite 'An avian pancreatic polypeptide modified by substitution of at least one amino acid residue ...' which is considered vague and indefinite."

The specification provides numerous working examples to teach how to make modified avian pancreatic polypeptides that bind to a protein molecule or a DNA molecule (see, e.g., pages 23-46). In addition, the specification provides various sequences of the

modified avian pancreatic polypeptides (see, e.g., the sequence listing), in particular, the Bcl2-binding aPP miniature proteins (e.g., Figure 4). Given the teachings of the specification and the knowledge in the art, a skilled artisan would have known the metes and bounds of the phrase "an avian pancreatic polypeptide modified by substitution of at least one amino acid residue." Reconsideration and withdrawal of rejections of claims 1, 19, and claims dependent therefrom under 35 U.S.C. § 112, second paragraph, are respectfully requested.

The Office Action further asserts that "[c]laims 6, 13, and all claims dependent therefrom recite the limitation 'which interaction with another molecule occurs' (claim 6)/ 'the interaction between the known protein and another molecule is inhibited' which is considered vague and indefinite" (Office Action, page 7, lines 4-9).

Applicants have canceled claim 6, thereby rendering the rejection moot. Applicants have amended claim 13 to clarify that the interaction is between the known protein and the Bcl2 protein. Applicants submit that these claims are clear and definite. Reconsideration and withdrawal of rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Priority Granted

Applicants note that the Examiner has granted priority to the provisional application No. 60/271,368, in view of Applicants' previous response.

Objection to Claims

The Office Action objects to claims 1-6, 12-13, and 23 for allegedly including non-elected sequences. Applicants respectfully disagree.

As described above, Applicants have amended independent claim 1 to more particularly delineate the claimed invention. Applicants also provided arguments above that claim 1 is a linking claim and the claimed invention should not be limited to SEQ ID NO: 23. Accordingly, the instant claims are directed to the same invention. Reconsideration and withdrawal of the objects are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7546. A one month petition for extension of time and payment of the appropriate fee are being filed concurrently herewith. Applicants request that any further fees or any credits be applied to **Deposit Account No. 18-1945, under Order No. YU-P01-027.**

Dated: July 20, 2005

Respectfully submitted,

By _____

Z. Angela Guo, Ph.D.
Registration No.: 54,144
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant